D2 Cont'd

c) an in vivo mizolastine release which prevents any plasma peak

d) a mizolastine bioavailability which is not decreased relative to that of an immediate release formulation; and

e) wherein the mizolastine comprises from 0.5% to 12% by weight of the tablet.

R E M A R K S

Entry of the preceding amendments and favorable reconsideration are respectfully requested in view of the preceding amendment and the following comments.

The amendment to amended claim 29 is entirely editorial in nature. The amendment to amended claim 31 finds complete antecedent support in the final paragraph on page 6 of the specification.

With the entry of the amendment to claim 29, the rejection of that claim under 35 U.S.C. 112, second paragraph has been completely overcome, thus clearly reducing issues and placing the application in better condition for appeal or for allowance.

In maintaining rejections based on a combination of references, the Examiner alleges:

> ... it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes

> into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The criteria for combining references has changed over the 31 years since the rendering of the *McLaughlin* opinion cited and relied upon by the Examiner. To assist the Examiner in this regard reference is respectfully made to the present criteria for combining references, as set forth in the *Dembiczak* Case, as quoted and cited on pages 6 and 7 of Applicants' Amendment of April 9, 2001. The Federal Circuit made it very clear in that case what the stringent current criteria are for combining references. In the event that any combination of references is maintained, the Examiner is respectfully asked to point out on the record how each of the current criteria is satisfied for each rejected claim by each combination of references instantly maintained.

The Federal Circuit has further clarified current practice in this regard in its opinion for *In re Lee*, 61 U.S.P.Q. 2d 1430 (Fed. Cir. 2002), at 1433 and 1434:

> "The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. ... "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed" ... the Examiner

> can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references" ... the Board rejected the need for "any specific hint or suggestion in a particular reference" to support the combination of ... references. Omission of a relevant factor required by precedent is both legal error and arbitrary agency action. ... "an agency rule would be arbitrary and capricious if the agency ... entirely failed to consider an important aspect of the problem".

As pointed out in the above quoted text, the Federal Circuit clearly and unequivocally stated in no uncertain terms that the standard relied upon by the Examiner is not the current standard and that "Omission of a relevant factor required by precedent is both legal error and arbitrary agency action." Current practice requires showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. These criteria have not been satisfied in the combination of references instantly relied upon in the present application.

The rejection of claims 21, 22, 24 to 26, 30 to 34, 38 and 39 "under 35 U.S.C. 103(a) as being unpatentable over US 4,590,062 (062) in combination with Desager et al. ..." is respectfully traversed in the same manner and for the same reasons as set forth on pages 4 and 5 of Applicants' Amendment of December

20, 2001. Attention is also respectfully directed to the significant comparison illustrated by Applicants' Figures 1 and 2.

Desager is only one of enumerable publications directed to antihistamines. The Examiner has failed to explain how one of ordinary skill in the art would be directed to combine teachings of Jang with Desager. If that hurdle could be overcome, the Examiner is still to explain what would lead the artisan specifically to mizolastine from antihistamines referred to by Desager. Even (purely arguendo and without admission) were one to find a reason for selecting Desager from a myriad of publications on antihistamines, all Desager would provide would be an invitation to experiment rather than an express teaching for combination.

What is even more important is that Desager gives no information concerning the formulation used. Therefore, it can not be meaningfully combined with, e.g., US 4,590,062 in any practical way. Moreover, in Desager's figure 2, page 424, the Cmax is nearly 400 ng/ml, as compared to Applicants' 243 ng/ml. It is clear from the foregoing that the purpose of lowering the peak in the plasma has been achieved by Applicants, and this without diminishing bioavailability.

Concerning sedative effects, please find herewith a copy of a publication: Hindmarch et al., *Clinical and Experimental Allergy*, Volume 29, Supplement 3, pp. 133 to 142, 1999, mentioning

that only a very limited number of antihistamines can claim to be free of sedative effects (see end of the abstract). Mizolastine has a ratio 1:N1 of 0.50 (weak effect - see Table 3, p. 139). Moreover in one test CRT, it seems that Mizolastine has been detected as having impairments (see p. 139).

Even the selection of the primary reference (Jang) is remote. The biologically active agents referred to by Jang include vitamins, analgesics, anorexics, anthelmintics, antiasthmatics, antibiotics, antiseptics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, anti-gout drugs, antifungals, anti-inflammatories, antimalarials, antimigraines, antimotion sickness drugs, antinauseants, antineoplastics, antitussives, decongestants, diuretics, muscle relaxants, sedatives, tranquilizers, as well as antihistamines and many others. Thus, even the selection of Jang as a primary reference is based solely on Applicants' own teachings. The entire combination of references can be regarded as nothing more than retrospective reconstruction.

Claim 21 is in the restricted "consisting essentially of" format, which separates it and dependent claim 22 even further from anything derivable by the two references combined by the Examiner.

All of claims 24 to 26 and 30 have the limitations of claim 24, which expressly calls for subject matter beyond anything that could be regarded as "obvious" from the teachings of the

applied art in the absence of Applicants' own disclosure. Claims 31 to 34, 38 and 39 all have the limitations of claim 31, which, once more, are not at all "obvious" from the references relied upon. The Examiner has not pointed out the particular text in each of the references that would actually lead one of ordinary skill in the art to each of the limitations of each claim so rejected.

The rejection of claims 23, 27 to 29, 35 to 37 and 39 to 43 "under 35 U.S.C. 103(a) as being unpatentable over US 4,590,062 (062) in combination with Desager et al. ... and further in view of US 5,102,666 (666)" is also respectfully traversed in the same manner and for the same reasons as discussed in the preceding remarks. Acharya (666) does not in any way overcome the noted deficiencies of the other two references.

Furthermore, claim 23 is in restricted "consisting essentially of" form, which makes it even more remote from anything derivable from the proposed combination of references.

Acharya is directed to controlled release compositions comprising calcium polycarbophil and an active agent selected from the group consisting of medicinal agents, breath fresheners and flavors. No rationale is found for combining any particular teaching of Acharya with those selected from the other references. The record explanation is entirely retrospective reconstruction. The vastness of the disclosures of each of the references minimizes

the possibility of anyone finding from the respective teachings subject matter called for by any of Applicants' claims.

Each of Applicants' claims has limitations which are not specifically addressed by the applied art. For any rejection retained for any of Applicants' claims, the Examiner is requested to apply the art to each limitation of each claim so rejected.

With regard to the rejection based on Jang in combination with Desager and Acharya, Applicants repeat by reference the rebuttal to that ground of rejection on pages 7 and 8 of the Amendment filed on December 20, 2001.

Having clearly reduced issues, entry of this Amendment is in order and is requested. Having overcome all outstanding grounds of rejection, favorable action on the merits and allowance of all of Applicants' claims are respectfully solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current Amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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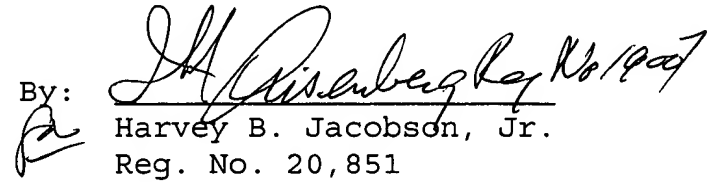
By: 
Harvey B. Jacobson, Jr.
Reg. No. 20,851

Enclosure: Hindmarch et al.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

29. (Amended) A sustained-release pharmaceutical dosage form according to claim [24] 28 wherein the ratio between the mizolastine and the L-tartaric acid is 0.5.

31.(Twice Amended) A coated sustained-release tablet having:

a) a core comprising mizolastine, a fatty matrix and an organic acid;

b) a dissolution profile which is pH independent; [and]

c) an in vivo mizolastine release which prevents any plasma peak

d) a mizolastine bioavailability which is not decreased relative to that of an immediate release formulation; and

[c)] e) wherein the mizolastine comprises from 0.5% to 12% by weight of the tablet.

Clinical and Experimental Allergy, 1999, Volume 29, Supplement 3, pages 133–142

Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects

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Summary

Behavioural changes are produced by any drug that enters the central nervous system. These psychoactive effects include changes in alertness, concentration, attention, memory, cognition, psychomotor accuracy, skilled performance and affect. Changes in psychological performance may affect the safety of both the individuals taking the drug and of those people coming into contact with them. The aims of psychopharmacological performance tests are to describe the nature, extent and severity of these changes and identify drugs without deleterious effects upon performance.

Use of traditional antihistamines has until recently been associated with a number of undesirable side-effects, the most troublesome of which is sedation. There are two aspects to sedation. Firstly, an objectively determined one based on the results of psychometric tests from controlled trials and secondly, the subjects response to the administration of a drug. Although the second generation of antihistamines have a much more favourable therapeutic index, use of these agents has also been reported to cause varying degrees of sedation. As antihistamines are largely used by ambulant patients, a complete evaluation of sedation should be performed through standardized objective tests, shown to be sensitive to the central effects of antihistamines as well as reliable ratings of subjective experiences.

An extensive review of the literature has identified a number of tests which appear to be sensitive to the central effects of antihistamines. These include tests of psychomotor performance, sensori-motor co-ordination speed, information processing, sensory skills as well as physiological measures and subjective rating scales.

Using this battery of cognitive and psychomotor tests, it is evident that only a very limited number of antihistamines can claim to be virtually free of both objective and subjective sedative effects, although the second generation of antihistamines are generally less impairing than the original ones; when prescribed at their recommended doses.

Keywords: CNS, psychoactive effects, sedation, antihistamines

Introduction

The use of traditional antihistamines such as diphenhydramine, hydroxyzine, promethazine and triprolidine is often associated with a number of unwanted and undesirable central side-effects, the most troublesome of which is sedation. The term 'sedation' usually expresses a wide range of subjective experiences described as drowsiness, loss of alertness, decreased concentration and somnolence, etc. In fact, sedation reflects the (measurable) impairment of superior cognitive functions such as attention, memory, co-ordination and psychomotor performance [1], which can severely impair daytime activities such as school performance, car driving ability, and many other tasks where concentration and a high degree of alertness and skill are required.

Excessive sedation following the use of traditional antihistamines, prompted the development of a second generation of specific H_1-receptor antihistamines that

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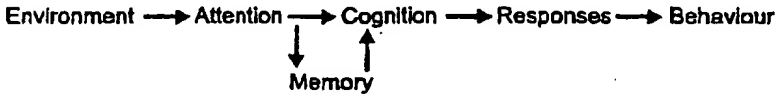

Fig. 1. An information processing model of cognition.

show a better tolerability at therapeutic doses and which have minimal effects on the central nervous system (CNS). The inability of these agents to cause sedation has been attributed to a number of factors including their low lipophilicity, which restricts their entry into the CNS [2]. The large molecular size, and greater affinity for peripheral H_1 receptors also reduces their propensity to cause sedation.

Although there are differences between various antihistamines in their ability to cause sedation, there are only a few antihistamines currently available that are claimed to be virtually free of sedative side-effects. Most antihistamines lack sedative effects when they are prescribed at the recommended therapeutic doses, however, sedation does occur when higher doses are used. As antihistamines are largely used by ambulant patients, including children, a complete and quantitative evaluation of sedation is required.

To measure the action of a drug on human behaviour, whether to assess the clinical change produced by drug treatment or to profile the pharmacodynamic activity of a particular drug, reliable and valid ratings and measurement systems need to be developed.

To examine the ways in which the activity of psychoactive drugs can be measured on psychomotor performance, Hindmarch [3] proposed a basic model of information processing, in which the human organism is regarded as an information-processing system, where sensory stimulation is processed and organized centrally, before being formed into motor response schemes which are ultimately realized in behaviour.

Figure 1 presents a simple model of information processing adapted from Hindmarch [3]. The model isolates the major processes as separate mechanisms within a linear system. Information from the environment is attended to and passed to higher cognitive mechanisms, where it is analysed and, if required, integrated with information from memory. A decision concerning appropriate response is then reached and an order passes to the response output mechanisms.

The choice of a psychomotor test is central to the understanding of any effects found. Thus, thorough psychopharmacological assessment requires a range of tests to ensure that subtle or specific drug effects are not overlooked. The clear need is for chosen tasks to be representative of key, well defined and accepted areas of cognition and psychomotor performance. Theoretically one should use a test battery where separate and conjoined aspects of performance are measured.

A cursory review of the literature reveals clearly that some 'tests' are more sensitive, valid and reliable than others, but it is also true that there is no single test than can satisfy all criteria in covering all aspects of human performance. A large number of trials have been carried out to investigate the central effects of antihistamines. In assessing this central effect, a large number of tests have been employed, however, many of these tests are not valid, have never been shown to be reliable, and the ability to reproduce the results is almost impossible. A number of steps can be taken to ensure the validity and reliability of an experiment, such as screening of volunteers prior to participation, however, the simplest way of ensuring the validity and reliability of an experiment is the inclusion of a verum (positive control). By inclusion of a verum, the sensitivity of the test battery is guaranteed so long as the verum scores show significant impairment. If following the use of a verum, effects are not obvious on an assessment measure, then it must be assumed that the test is insensitive and no credance can be given to any findings obtained in such an instance. Antihistamines such as promethazine, hydroxyzine, clemastine and triprolidine have been commonly and consistently shown to impair performance on a wide range of tests [2]. For this reason, they are frequently included in studies as positive internal controls, when investigating the central effects of antihistamines.

This review will aim to identify the tests which are most sensitive to the effects of antihistamines. Its primary purpose is to identify a test battery which can be used when assessing the sedative profile of antihistamines. A secondary objective of this review is to assess the sedative potential of second generation of antihistamines using this battery f cognitive and psychomotor tests.

Methods

A computer-assisted MEDLINE search was conducted to identify well-designed studies, published from 1965 to 1997, investigating the sedative, psychomotor and cognitive effects of all antihistamines that are either available or soon to be available. Search terms included histamine H_1 antagonists, antihistamines, psychomotor performance, cognitive function, and specific drug names such as astemizole, loratadine, cetirizine, fexofenadine, mizolastine and ebastine. The search was limited to studies performed in humans. Studies had to be placebo and verum controlled, performed in healthy volunteers, and of particular interest

were studies using standardized, quantitative methods of defining both objective and subjective drug-induced effects on sedation, psychomotor performance and cognition. As well as publications, data have also been included from published abstracts in peer-reviewed journals.

Results

A total of 55 placebo and verum-controlled studies were reviewed. This comprised data on a total of 21 antihistamines, of which 14 are classed as second-generation non-sedating antihistamines. Seven traditional antihistamines were reviewed and they were almost always included in these studies as positive controls. Both acute (A) and repeated (R) dosing regimens were included. All studies used a double-blind cross-over design, and single-blind cross-overs or parallel group comparison methods were excluded.

The categorization of tests is similar to that performed by Rombaut & Hindmarch [4], in which tests measuring similar CNS activities were grouped together.

For each drug and test dose, results have been listed as 'impairment' or 'no impairment' for each test (using the codes presented in Table 2). If a statistically significant difference ($P<0.05$, $P<0.01$ or better) between the test drug and placebo was found on a specific test indicating a disturbed CNS activity, then the results were listed as 'impairment'.

In addition, for each antihistamine a risk : benefit ratio was calculated similar to that conducted by Hindmarch [5]. For each drug, the number of discrete tests in which significant impairment was reported were totalled. The risk : benefit ratio for each antihistamine was then calculated according to the following formula: I ÷ NI, where I = the number of tests where significant impairment of performance was found, and NI = the number of tests where no impairment was detected. This calculation gives an impairment : no impairment ratio which represents the likelihood that a given antihistamine will cause sedative effects. The more impairment observed with a given drug, the greater is the value of the ratio. Conversely, an antihistamine with a good benefit : risk ratio will have a value close to zero.

It is evident from these studies, which are considered to be the most adequately controlled, that most of the antihistamines under investigation do possess some sedative activities. However, it is the first generation antihistamines which consistently impair performance at all doses tested, whereas the second generation of antihistamines have a generally lower sedation index, although there are differences between the drugs.

However, the most important finding is that the traditional antihistamines included as positive controls behave as expected in that they consistently impair performance on a large number of tests measuring different aspects of cognitive and psychomotor performance. This impairment is noticed on both objective and subjective measures.

Chlorpheniramine (4–16 mg), diphenhydramine (25–150 mg), hydroxyzine (25 and 50 mg) and promethazine (10, 25 and 30 mg) were exclusively used as verums, whereas clemastine (1–4 mg) and ketotifen (1 and 2 mg) were included in a number of studies as a comparator rather than a positive control.

Triprolidine was included in a total of 18 studies as a positive control and resulted in impairment of all aspects of cognitive and psychomotor performance at all doses tested.

There was one incidence in which no impairment was noted with a 10-mg dose of triprolidine, however, this was a subjective assessment of sedation, and it is widely accepted that subjective reports of sedation are not as reliable as objective tests. Subjects often fail to report sedation even though there is evidence of an objective impairment and subjects even report sedation with no objective evidence of cognitive disruption.

Diphenhydramine was included in a total of 18 studies, and impairing effects were noted with all doses under investigation, with the exception of one study, where no impairments were noted. However, in this study assessments were made only at 2 h post-drug ingestion and it is possible that impairing effects would have been evident had the testing been continued for longer than 2 h.

All other traditional antihistamines behaved generally as expected, and although there are instances where no impairment has been reported, the number of studies reporting impairing effects far exceeds those which have failed to detect sedation.

Discussion

Perhaps the most important finding from the studies reviewed, is that the inclusion of a verum is essential when investigating the CNS activity of newly developed antihistamines. In a study that involves only the test drug and placebo, data showing no change in test scores may indicate either that the drug does not induce impairment or that the tests lacked sufficient sensitivity to detect the impairment. Inclusion of the positive control guarantees the sensitivity of the test battery. The positive control should be an antihistamine known to be impairing, given at the lowest dose that will produce changes in test scores. Higher doses are sometimes used, however, this would leave open for question whether the endpoints of CNS effects would have been sensitive enough to detect lesser but relevant effects of the test drug. By using the minimal dose of the verum needed to produce CNS effects as a positive control, there is a greater confidence in the sensitivity of the

Table 1. Placebo- and verum-controlled studies

Drug	Test results: Dose	No impairment	Impairment	References
Acrivastine	4 mg (A)	B7, E2, H1		15
	8 mg (A)	A1, 3B7, 2E2, 2H1		15, 16, 17
	16 mg (A)	B7, E2, H1	A1, B7	15, 17
	24 mg (A)		A1, B7	17
Astemizole	10 mg (A)	B4, C1, E4, G2, G4, 2H1		11, 18, 19, 20
	20 mg (A)	B4, H1		19
	30 mg (A)	A2, C1, H1		21
	40 mg (A)	C4, H1		22
Azatadine	4 mg (A)	A2, B5, H1		23
	8 mg (A)	H1	A2, B5	23
Cetirizine	2.5 mg (A)	B5, C1, G5, H1		24*
	5 mg (A)	3A2, B5, B7, C1, 2C2, E1, G3, G5, 3H1, H3	B1, H1, H3	7, 10, 24*, 25, 26
	10 mg (A)	A1, 3A2, B1, B5, B7, 3C1, 2C2, 2C5, D1, 2G4, G5, 9H1, H3,	E1, E5, G3, 2H1, H3	7, 10, 13, 18, 24*, 25, 26, 27, 28, 29, 31
	10 mg (R)	A1, D1, E5, G1, G2, G3, 2H1		14, 30, 31
	15 mg (A)	E1	B1, G3, H1, H3	26
	20 mg (A)	3A2, B7, 2C1, 2C5, 3H1, H3	2C2	7, 10, 25, 29
	20 mg (R)	G1, H1		14
Chlorpheniramine	4 mg (A)	H1	A2, B3, 2B4, 2B5, C3, D1, 2H1, H3	23, 32, 33, 34
	8 mg (A)		2G4, 2H1	35, 36
	12 mg (A)		A2, C1, H1	21
	12 mg (R)	B7, C1	G1, 2H1	14, 37
	16 mg (A)		C4, H1	22
Clemastine	1 mg (A)	C3, 2H1	B1, B4, B7, D2	33, 38, 39
	2 mg (A)		A1, B2, 2B5, 2B8, 2C1, E2, G1, 2H1	40, 41, 42
	3 mg (A)		3, H1	38
	4 mg (R)		A1, E3	43
Diphenhydramine	25 mg (A)		B3, B4, B5, C3, D1, H1, H3	32, 34
	50 mg (A)		A1, 3A2, B2, 2B3, 2B5, 3B7, 2C2, C7, E1, 3E2, G1, 3G4, 10H1, 3H3	7, 8, 10, 16, 17, 18 25, 27, 32, 44, 45,
	100 mg (A)	B7, C1	H1	46
	100 mg (R)		C1, C2, E2, H1	47
	150 mg (A)		G3	12
	150 mg (R)		C2, E5, 2G3, H1, H3	30, 48
Ebastine	10 mg (A)	B1, B8, G1, H1		42
	10 mg (R)	A1, H1		49
	20 mg (A)	B1, B8, G1, H1		42
	20 mg (R)	A1, H1		49
	30 mg (R)	A1, H1		49
Fexofenadine	80 mg (A)	B5, C1, G5, H1		50
	120 mg (A)	B3, B5, C1, C2, E1, G3, G5, 2H1		50, 51
	120 mg (R)	A1, E3		43
	180 mg (A)	B3, B5, C1, C2, E1, G3, G5, 2H1		50, 51
	240 mg (A)	B3, C2, E1, G3, H1		51
	240 mg (R)	A1, E3		43

Table 1. continued

Drug	Test results: Dose	No impairment	Impairment	References
Hydroxyzine	25 mg (A)		2C1, 2C5, E5, 3H1	13, 25, 29
	50 mg (A)		G4, H1	27
	50 mg (R)		B5, B6, H1	52
Ketotifen	1 mg (A)		H1	28
	2 mg (A)	G4	H1	18
Levocabastine	0.5 mg/mL (A)	A3, C1, D1, H1		53
	2 mg/ML (A)	A3, C1, D1, H1		53
Loratadine	10 mg (A)	A1, B4, 2B5, 2C1, C2, D1, E4, G4, 2G5, 5H1	B1, B7, D2	18, 24, 39, 50, 54, 55
	10 mg (R)	C2, G3, H3		48
	20 mg (A)	A1, B4, B5, C1, C2, D1, E4, G5, 3H1		24, 54, 55
	20 mg (R)		A1, E2, H1	56
	40 mg (A)	B4, C1, D1, 2H1	B5, C2, E4, G5	24, 54
	40 mg (R)	C2, H3	G3	48
Mequitazine	5 mg (A)	C1, C2, E4, H1	B4	57
	10 mg (A)	C1, E4, H1	B4, C2	57
Mizolastine	5 mg (A)	A1, A2, B2, B3, 3B5, 3C1, C5, D1, E2, 2H1		41, 58, 59
	10 mg (A)	A1, B2, 2B5, 2C1, E2, H1		40, 41
	15 mg (A)	A2, B3, 2B5, 2C1, C5, D1, H1		58, 59
	20 mg (A)		A1, B2, B5, C1, H1	41
	40 mg (A)		A1, B2, B5, C1, H1	41
	45 mg (A)	B5, H1	A2, B3, B5, 2C1, C5, D1 H1	58, 59
Oxatomide	30 mg (A)		2B3, B4, C2, 2E1, 2G3, 2H1, H3	28
Promethazine	10 mg (A)	H1	B5, C1, G5, H1	26, 33, 51
	25 mg (A)		B5, C1, G5	24
	30 mg (A)	H1		50
Tazyfylline	5 mg (A)	B4, C1, C2, E4, H1		60
	10 mg (A)	C1, C2, E4, H1	B4	60
	15 mg (A)	C1, C2, H1	B4, E4	60
Temelastine	200 mg (R)	C1, C2, E2, H1		47
Terfenadine	20 mg (A)	C3, H1		38
	60 mg (A)	2A1, B2, 2B3, 5B4, 2B5, 3B7, 6C1, 4C2, 2C3, C7, D1, E1, E2, E3, 3E4, G1, 3G4, 16H1, H3	A2, B3, B5, B7, C1, C5, D1, D2, G4	8, 11, 17, 18, 19, 32, 33, 34, 35, 36, 38, 39, 44, 45, 46, 55, 57, 58, 59, 60, 61
	60 mg (R)	A1, H1		62
	120 mg (A)	2A1, B4, 2B7, C1, C2, C4 D1, E4, G3, 3H1	G1, H1	12, 17, 31, 46, 60
	120 mg (R)	A1, B5, B6, B7, C1, G1, G2, 3H1	A1, D1, E2, H1	14, 31, 37, 52, 56
	180 mg (A)	A1, B7		17
	240 mg (A)	B7, C1, H1		46
Triprolidine	2.5 mg (A)		B7, E2, G2, H1	15, 20
	5 mg (A)		B7, E2, H1	15
	5 mg (R)		A1, E2, H1	56
	7.5 mg (A)		B6, C1, C2, H1	61
	10 mg (A)	H1	2A1, A2, A3, B2, 4B4, 2B5, 6C1, 4C2, C5, 4D1, 4E4, 7H1	11, 19, 31, 53, 54, 55, 57, 58, 59, 60
	10 mg (R)		3A1, D1, G2, 2H1	31, 49, 62
	15 mg (R)		G1, H1	14

Table 2. Codes for measures of performance

A: Psychomotor performance	
A1:	Actual car driving
A2:	Simulated car driving
A3:	Simulated car tracking
B: Sensorimotor co-ordination speed	
B1:	Adaptive tracking
B2:	Critical tracking
B3:	Continuous tracking
B4:	Visuo-motor co-ordination
B5:	Choice reaction time
B6:	Simple reaction time
B7:	Reaction time
B8:	Pursuit rotor
C: CNS arousal, information processing	
C1:	Critical flicker fusion
C2:	Digit symbol substitution task
C3:	Mental arithmetic
C4:	Letter cancellation
C5:	Stroop colour test
C6:	Logical reasoning
C7:	Visual search task
D: Memory	
D1:	Short-term memory
D2:	Continuous memory task
E: Sensory skills	
E1:	Vigilance task
E2:	Attention task
E3:	Continuous attention task
E4:	Dynamic visual acuity
E5:	Simulated assembly-like task
F: Motor ability	
F1:	Finger tapping
G: Physiological	
G1:	Electroencephalograph (EEG)
G2:	Continuous EEG
G3:	Multiple sleep latency test
G4:	Evoked potentials
G5:	Actigraphy
H: Subjective ratings	
H1:	Visual analogue rating scales
H2:	Profile of moods scale
H3:	Stanford sleepiness scale

measurements of mental performance [6]. It is important to recognize that the purpose of the inclusion of the positive control is not to draw direct comparisons with the test drug. The study drug should be compared to placebo, and the positive control should be used only to ensure the sensitivity of the psychometrics in the particular instance of that study.

In addition it is important to include tests which measure different aspects of cognitive and psychomotor performance. Rombaut & Hindmarch [5] demonstrated clearly that a large number of tests are available and currently in use when investigating the central effects of antihistamines. However, most of the tests are not reliable, have never been validated and reproduction of the results is almost impossible, even when experiments are carried out in the same laboratory.

It is possible that various psychometric tests may have a differential sensitivity to the sedative effects of antihistamines and it is for this reason that a battery of tests must be utilized in order to assess the activity of these compounds.

It appears that tests of car driving, whether it is actual highway car driving or a simulated car-driving task, are commonly utilized when assessing the sedative profile of antihistamines. Tests of car driving feature in 15 studies and appear to be sensitive to the sedative effects of antihistamines. It has been suggested that the ability of the driver to control weaving of the car, measured as the standard deviation of the lateral position, is an indicator of drug-induced sedation [7]. Such tests represent low level global motor performance and do not assess more important functions, e.g. attention, judgement, cross-over ordination reflexes memory, etc. Car-driving tests *per se* are not always a suitable choice for children and non-driving patients and to assess the potential of an antihistamine to interfere with mental performance, studies should incorporate several sensitive and reliable laboratory tests that assess an array of mental processes.

A task which has commonly featured in studies investigating the central effects of antihistamines is the critical flicker fusion (CFF) task. CFF features in 16 studies and has consistently demonstrated the reduction in cognitive capacity following traditional antihistamines, as well as detecting changes following other antihistamines, e.g. loratadine and cetirizine, where other tests have failed to detect any impairment. CFF is one of the most commonly used tasks in the area and has proved sensitive to a wide range of compounds. The advantages of CFF include the simple, non-invasive nature of the test, the short duration of the assessment and an absence of major practice effects (subject to training subjects prior to participation in the study) [8]. For this reason, it is recommended that CFF be included in all test batteries when investigating the central effects of antihistamines.

One of the most popular measures of sensory motor performance is reaction time to a critical stimulus. Choice reaction time (CRT) is used as an indicator of sensorimotor response, assessing the efficiency of the attentional and response mechanisms in the information processing chain without the need for extended cognitive processing. The total reaction time is regarded as the sum of two separable components: the stimulus recognition reaction time (RRT) used as a measure of attentional monitoring, and the motor reaction time (MRT) used as a

Table 3. Ranked sedative effects of selected antihistamines using I : NI ratio

Drug	Dose	No. tests showing no impairment (NI)		No. tests showing impairment (I)	
		Objective	Subjective	Objective	Subjective
Fexofenadine	80 mg	3	1		
	120 mg	9	2		
	180 mg	7	2		
	240 mg	6	1		
Ratio I : NI: total = 0.00, subjective = 0.00, objective = 0.00					
Ebastine	10 mg	4	2		
	20 mg	4	2		
	30 mg	1	1		
Ratio I : NI: total = 0.00, subjective = 0.00, objective = 0.00					
Cetirizine	2.5 mg	3	1		
	5 mg	11	4	1	2
	10 mg	24	12	3	3
	15 mg	1		2	2
	20 mg	9	5	2	
Ratio I : NI: total = 0.21, subjective = 0.32, objective = 0.17					
Loratadine	10 mg	14	6	3	
	20 mg	8	3	2	1
	40 mg	4	3	5	
Ratio I : NI: total = 0.29, subjective = 0.07, objective = 0.38					
Mizolastine	5 mg	13	2		
	10 mg	7	1		
	15 mg	8	1		
	20 mg			4	1
	40 mg			4	1
	45 mg	1	1	7	
Ratio I : NI: total = 0.50, subjective = 0.40, objective = 0.52					
Chlorpheniramine	4 mg	1		8	3
	8 mg			2	2
	12 mg	2		3	3
	16 mg			1	1
Ratio I : NI: total = 7.67, subjective = not done, objective = 4.67					
Diphenhydramine	25 mg			5	2
	50 mg			23	13
	100 mg		2	3	2
	150 mg			5	2
Ratio I : NI: total = 27.50, subjective = not done, objective = 18.0					
Triprolidine	2.5 mg			3	1
	5 mg			4	2
	7.5 mg			3	1
	10 mg		1	35	9
	15 mg			1	1
Ratio I : NI: total = 60.00, subjective = 14.00, objective = not done					

measure of the efficiency of the response output system. Measurements of CRT provide information on the constant, very rapid adjustments individuals must make to their environment, which require them to attend to several potential stimuli at once [9]. This suggests that there is a high degree of construct validity inherent in reaction time measures. CRT appears in 17 studies and the sensitivity of the test is highlighted by the fact that it is one of the few tests that detected impairments with antihistamines, such as mizolastine, cetirizine and loratadine.

The Digit Symbol Substitution Test (DSST), a simple pencil and paper test, is reported to measure integration, speed and accuracy of visual and fine motor skills [9]. Due to its simplicity, DSST is employed in a large number of studies and appears to be a reliable indicator of sedation.

Other objective measures of performance which appear commonly in the literature are tests such the P300 which represent the endogenous component of the auditory evoked potential [10]. This test is more dependent on information processing demands imposed by the tasks than on the physical attributes of the test and the prolongation of the P300 is taken as an index of impaired cognitive function. The multiple sleep latency test is also used throughout the day to provide an objective index of sleepiness [11].

In addition to objective measures of performance, subjective reports are also frequently utilized. Self-assessments of performance and sleepiness, although commonly used and relatively easy to administer, are not as straightforward or reliable as objective measures of sedation. Subjective reports are much more likely to be influenced by transient fluctuations and other factors such as demand characteristics and environmental stimuli than are objective measures of performance [12]. Subjective reports are extremely unreliable, because by their very nature, sleepiness, somnolence and sedation can impair the self assessment of awareness and thus result in misleading results. Despite these inconsistencies, if subjective measures are combined with sensitive and reliable objective tests, they can provide useful data. Almost all the studies reviewed, have employed subjective rating scales, however, conflicting data are reported and conclusions about the sedative potential of an antihistamine must not be made solely on data from subjective tests.

One well known problem with performance-based measures in psychopharmacology is that individuals can compensate for the effects of a psychoactive compound by changing their performance strategy and/or motivation levels. Performance testing is often intermittent and subjects are usually forewarned or aware of the experimental protocol and the impeding test. This allows subjects to prepare themselves for performance assessment. The limited period of concentration required may not accurately reflect typical levels of alertness throughout the day [13].

One way of overcoming the problems associated with the use of fixed test intervals is to use actigraphy to monitor the behaviour throughout the day. Actigraphy provides a continuous measurement of the motor component of behaviour and is thus able to detect impairments in performance throughout the day and so overcomes the problems associated with fixed time interval testing [14].

The secondary objective of this review was to assess the sedative potential of second-generation antihistamines using this battery of cognitive and psychomotor tests. Using the formula of I ÷ NI to calculate the risk : benefit ratio for a number of antihistamines, it is possible to rank these drugs in order of increasing adverse effects. Table 3 identifies only a few antihistamines with a risk : benefit ratio of zero. These include astemizole (10–60 mg), ebastine (10–30 mg), fexofenadine (80–240 mg), levocabastine (0.5–2.0 mg/mL) and temelastine (200 mg). As for levocabastine and temelastine, only a small number of studies have investigated the CNS effect of these compounds and although the I : NI ratio is calculated as zero, this value is derived from one or two studies, and therefore further research is required before they can be confidently placed in the nonsedating antihistamine category.

Fexofenadine, which is the active metabolite of terfenadine, is a recent addition to the list of non-sedating antihistamines. A number of placebo and verum controlled studies have been conducted using fexofenadine at up to four times the recommended dose. Within these dose ranges, fexofenadine lacks any objectively determined sedative activity and does not impair cognitive and psychomotor performance.

Conclusion

It is evident from the findings of this review that all antihistamines possess a potential to produce either objective or subjective sedation or both. This potential is a function of histaminergic mechanisms involved in the control of CNS arousal and is more likely to happen with those substances which cross the blood–brain barrier and exert a direct effect on the brain. In order to be able to detect this possible sedative activity, it is important to use a battery of tests which have proved to be sensitive and reliable indicators of sedation.

A number of tests have been identified which are sensitive to both objective and subjective effects of antihistamines. These include CFF, CRT, DSST, and actual and simulated car driving. Physiological measures such as the MSLT and the use of evoked potentials can also be added to the test battery depending on the requirements of a specific study. The use of actigraphy could enhance the chances of detecting sedation as it provides an index of sedation on a continuous 24-h basis.

Using this battery of tests, data from the present review clearly demonstrates that the second generation of antihistamines have a much more favourable behavioural toxicity than their predecessors and represent a major advance in the treatment of allergy in ambulant patients who wish to continue with their activities f daily living without experiencing decrements in their cognitive and psychomotor abilities.

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